**Supplemental Table 1.**

**Pooled hazard ratios of colorectal cancer according to BCAA intake after adjustment for covariates and dietary factors**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Quintile of BCAA intake |  |  |
| Q1  | Q2 | Q3 | Q4 | Q5 | P for trend |
|  Pooled analysis |  |  |  |  |  |  |
| Model 1 HR | 1.00 | 0.98 (0.87, 1.10) | 0.97 (0.87, 1.08) | 0.97 (0.87, 1.08) | 0.89 (0.80, 1.00) | 0.06 |
| Model1 + calcium (total) | 1.00 | 1.00 (0.90, 1.11) | 0.99 (0.89, 1.11) | 0.99 (0.88, 1.12) | 0.92 (0.82, 1.04) | 0.16 |
| Model1 + red meat | 1.00 | 0.97 (0.88, 1.06) | 0.97 (0.87, 1.08) | 0.96 (0.86, 1.07) | 0.89 (0.79, 0.99) | 0.06 |
| Model1 + processed meat | 1.00 | 0.98 (0.88, 1.09) | 0.97 (0.87, 1.08) | 0.97 (0.87, 1.08) | 0.90 (0.80, 1.01) | 0.07 |
| Model1 + turkey and chicken | 1.00 | 0.99 (0.87, 1.12) | 0.98 (0.88, 1.10) | 0.97 (0.87, 1.09) | 0.90 (0.79, 1.02) | 0.09 |
| Model1 + fish | 1.00 | 0.99 (0.88, 1.12) | 0.98 (0.88, 1.10) | 0.98 (0.88, 1.10) | 0.91 (0.80, 1.02) | 0.14 |
| Model1 + total dairy intake | 1.00 | 1.00 (0.90, 1.11) | 0.99 (0.88, 1.10) | 0.98 (0.87, 1.10) | 0.92 (0.81, 1.03) | 0.13 |
| Model1 + dairy calcium | 1.00 | 1.01 (0.90, 1.12) | 1.01 (0.90, 1.13) | 1.02 (0.91, 1.14) | 0.96 (0.85, 1.08) | 0.50 |
| Model1 + non-dairy calcium | 1.00 | 0.99 (0.87, 1.12)  | 0.98 (0.88, 1.09) | 0.97 (0.87, 1.09) | 0.90 (0.80, 1.01) | 0.08 |
| Model1 + vitamin D | 1.00 | 1.04 (0.88, 1.23) | 0.98 (0.88, 1.09) | 0.98 (0.88, 1.09) | 0.91 (0.81, 1.02) | 0.14 |
| Model1 + folate | 1.00 | 0.99 (0.88, 1.10) | 0.98 (0.88, 1.09) | 0.98 (0.88, 1.09) | 0.91 (0.81, 1.02) | 0.11 |
| Model1 + fiber | 1.00 | 0.98 (0.86, 1.11) | 0.97 (0.87, 1.08) | 0.97 (0.87, 1.08) | 0.89 (0.80, 1.00) | 0.09 |
| Model2+ history of diabetes | 1.00 | 1.00 (0.90, 1.12) | 1.01 (0.90, 1.12) | 1.01 (0.90, 1.13) | 0.95 (0.84, 1.07) | 0.40 |

Abbreviations HR: hazard ratio CI: confidence interval SD: standard deviation BCAA: branched chain amino acid.

Pooled HRs were calculated by pooling HRs in HPFS, NHS and NHS2 using random effect models.

Multivariable HRs (Model 1) were adjusted for age, smoking status (never, past, current <15 pack-years, current ≥15 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), regular aspirin use (≥2 tablets/week, yes or no), menopausal status and postmenopausal hormone use (premenopause, never, past, current, in women only), body mass index (<23, 23 to <25, 25 to <27, 27 to <30, ≥30 kg/m2), physical activity (quintile), alcohol consumption (0 to <5, 5 to <10, 10 to <15, or ≥15 g/day).

**Supplemental Table 2**.

**Pooled hazard ratios (95% CI) of colorectal cancer according to cumulative average intake [per standard deviation (SD)] of BCAAs by sub-sites**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | NHS |  | HPFS |  | NHSII |  | Pooled |  |
|   | Per SD | p-value | Per SD | p-value | Per SD | p-value | Per SD | p-value |
| Proximal | 0.98 (0.91, 1.07) | 0.68 | 1.00 (0.91, 1.11) | 0.96 | 0.98 (0.76, 1.26) | 0.86 | 0.99 (0.93, 1.05) | 0.75 |
|  |  |  |  |  |  |  |  |  |
| Distal | 1.03 (0.93, 1.14) | 0.55 | 0.87 (0.78, 0.97) | 0.01 | 1.20 (0.96, 1.49) | 0.11 | 1.00 (0.85, 1.18) | 0.98 |
|   |  |  |  |  |  |  |  |  |
| Rectum | 0.89 (0.78, 1.00) | 0.06 | 1.04 (0.91, 1.18) | 0.51 | 0.93 (0.73, 1.20) | 0.58 | 0.96 (0.85, 1.07) | 0.43 |

Abbreviations HR: hazard ratio CI: confidence interval SD: standard deviation BCAA: branched chain amino acid, NHS: Nurses’ Health Study, NHS II: Nurses’ Health Study II, HPFS: Health Professionals Follow-up Study.

Multivariable HRs were adjusted for age, smoking status (never, past, current <15 pack-years, current ≥15 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), regular aspirin use (≥2 tablets/week, yes or no), menopausal status and postmenopausal hormone use (premenopause, never, past, current, in women only), body mass index (<23, 23 to <25, 25 to <27, 27 to <30, ≥30 kg/m2), physical activity (quintile), alcohol consumption (0 to <5, 5 to <10, 10 to <15, or ≥15 g/day) and dairy calcium intake (quintile). P for trend was calculated using the median value of each quintile category. Standard deviation (SD) was 2.59 g/d in HPFS, 1.98 g/d in NHS and 2.47 g/d in NHS II. Pooled HRs were calculated by pooling HRs in HPFS, NHS and NHSII using random effect models.

**Supplemental Table 3.**

**Hazard ratios of distal and rectal cancer according to BCAA intake after adjustment for covariates and dietary factors**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Quintile of BCAA intake |  |  |
| Q1  | Q2 | Q3 | Q4 | Q5 | P for trend |
|  HPFS-distal colon cancer |  |  |  |  |  |  |
| Model 1 HR | 1.00 | 0.86 (0.63, 1.16) | 0.71 (0.51, 0.97) | 0.80 (0.58, 1.09) | 0.71 (0.52, 0.99) | 0.04 |
| Model1 + calcium (total) | 1.00 | 0.89 (0.65, 1.20) | 0.74 (0.54, 1.03) | 0.84 (0.61, 1.16) | 0.75 (0.54, 1.05) | 0.10 |
| Model1 + red meat | 1.00 | 0.87 (0.64, 1.18) | 0.72 (0.52, 0.99) | 0.81 (0.59, 1.11) | 0.73 (0.52, 1.01) | 0.05 |
| Model1 + processed meat | 1.00 | 0.85 (0.63, 1.16) | 0.70 (0.51, 0.97) | 0.80 (0.59, 1.10) | 0.73 (0.53, 1.01) | 0.06 |
| Model1 + turkey and chicken | 1.00 | 0.87 (0.64, 1.18) | 0.71 (0.51, 0.99) | 0.79 (0.57, 1.10) | 0.69 (0.48, 0.99) | 0.05 |
| Model1 + fish | 1.00 | 0.84 (0.62, 1.14) | 0.69 (0.50, 0.96) | 0.78 (0.56, 1.08) | 0.70 (0.49, 0.99) | 0.04 |
| Model1 + total dairy intake | 1.00 | 0.85 (0.63, 1.16) | 0.71 (0.52, 0.98) | 0.80 (0.58, 1.10) | 0.71 (0.52, 0.99) | 0.04 |
| Model1 + dairy calcium | 1.00 | 0.88 (0.65, 1.19) | 0.73 (0.53, 1.01) | 0.84 (0.61, 1.15) | 0.76 (0.54, 1.06) | 0.11 |
| Model1 + non-dairy calcium | 1.00 | 0.86 (0.63, 1.16) | 0.71 (0.51, 0.98) | 0.81 (0.59, 1.11) | 0.73 (0.52, 1.01) | 0.05 |
| Model1 + vitamin D | 1.00 | 0.86 (0.63, 1.16) | 0.71 (0.51, 0.98) | 0.80 (0.58, 1.10) | 0.72 (0.51, 1.02) | 0.06 |
| Model1 + folate | 1.00 | 0.86 (0.64, 1.17) | 0.71 (0.52, 0.98) | 0.81 (0.59, 1.11) | 0.73 (0.52, 1.00) | 0.05 |
| Model1 + fiber | 1.00 | 0.86 (0.64, 1.17) | 0.72 (0.52, 0.99) | 0.81 (0.59, 1.10) | 0.72 (0.52, 0.99) | 0.04 |
|  |  |  |  |  |  |  |
|  NHS-rectal colon cancer |  |  |  |  |  |  |
| Model 1 HR | 1.00 | 0.82 (0.59, 1.14) | 0.88 (0.63, 1.21) | 0.78 (0.56, 1.10) | 0.77 (0.54, 1.09) | 0.14 |
| Model1 + calcium (total) | 1.00 | 0.83 (0.60, 1.15) | 0.89 (0.64, 1.23) | 0.80 (0.56, 1.13) | 0.80 (0.56, 1.16) | 0.24 |
| Model1 + red meat | 1.00 | 0.82 (0.59, 1.14) | 0.87 (0.63, 1.21) | 0.78 (0.55, 1.10) | 0.77 (0.54, 1.09) | 0.13 |
| Model1 + processed meat | 1.00 | 0.82 (0.59, 1.14) | 0.87 (0.63, 1.21) | 0.78 (0.55, 1.09) | 0.77 (0.54, 1.09) | 0.13 |
| Model1 + turkey and chicken | 1.00 | 0.85 (0.61, 1.18) | 0.91 (0.65, 1.27) | 0.82 (0.57, 1.17) | 0.81 (0.55, 1.19) | 0.30 |
| Model1 + fish | 1.00 | 0.84 (0.60, 1.16) | 0.89 (0.64, 1.25) | 0.79 (0.56, 1.13) | 0.77 (0.52, 1.12) | 0.17 |
| Model1 + total dairy intake | 1.00 | 0.83 (0.60, 1.15) | 0.89 (0.64, 1.23) | 0.80 (0.56, 1.13) | 0.80 (0.56, 1.16) | 0.24 |
| Model1 + dairy calcium | 1.00 | 0.83 (0.60, 1.16) | 0.90 (0.64, 1.26) | 0.81 (0.57, 1.16) | 0.81 (0.55, 1.18) | 0.28 |
| Model1 + non-dairy calcium | 1.00 | 0.82 (0.59, 1.14)  | 0.87 (0.63, 1.21) | 0.78 (0.55, 1.09) | 0.77 (0.54, 1.09) | 0.14 |
| Model1 + vitamin D | 1.00 | 0.82 (0.59, 1.14) | 0.88 (0.64, 1.22) | 0.79 (0.56, 1.11) | 0.79 (0.56, 1.13) | 0.19 |
| Model1 + folate | 1.00 | 0.83 (0.60, 1.15) | 0.89 (0.64, 1.23) | 0.80 (0.57, 1.13) | 0.81 (0.57, 1.15) | 0.23 |
| Model1 + fiber | 1.00 | 0.83 (0.60, 1.15) | 0.89 (0.64, 1.23) | 0.80 (0.57, 1.12) | 0.79 (0.55, 1.12) | 0.18 |

Abbreviations HR: hazard ratio CI: confidence interval SD: standard deviation BCAA: branched chain amino acid.

Pooled HRs were calculated by pooling HRs in HPFS, NHS and NHS2 using random effect models.

Multivariable HRs (Model 1) were adjusted for age, smoking status (never, past, current <15 pack-years, current ≥15 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), regular aspirin use (≥2 tablets/week, yes or no), menopausal status and postmenopausal hormone use (premenopause, never, past, current, in women only), body mass index (<23, 23 to <25, 25 to <27, 27 to <30, ≥30 kg/m2), physical activity (quintile), alcohol consumption (0 to <5, 5 to <10, 10 to <15, or ≥15 g/day).

**Supplemental Table 4.**

**Pooled hazard ratios (95% CI) of colorectal cancer risk according to quintiles of BCAA intake stratified by lifestyle factors**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| Per SD increment1 | P value | P for interaction |
| BMI (kg/m2) |  |  | 0.75 |
| <25 | 0.98 (0.93, 1.04) | 0.60 |  |
| >25 | 0.99 (0.91, 1.08)  | 0.82 |  |
| Smoking (pack-year) |  |  | 0.17 |
| never | 0.98 (0.93, 1.04) | 0.45 |  |
| <20  | 0.93 (0.85, 1.01) | 0.07 |  |
| 20+  | 0.95 (0.89, 1.02) | 0.16 |  |
|  |
| Alcohol intake (g/d) |  |  | 0.34 |
| 0-5  | 0.97 (0.92, 1.01) | 0.17 |  |
| 5-15  | 1.03 (0.94, 1.12) | 0.59 |  |
| 15+  | 0.95 (0.83, 1.08) | 0.40 |  |
|  |
| Physical activity (MET-hours/wk)2 |  | 0.84 |
| <median | 0.96 (0.91, 1.01) | 0.09 |  |
| >median | 1.00 (0.92, 1.08) | 0.91 |  |
|  |  |  |  |
| Animal/vegetable protein ratio |  |  | 0.78 |
| <median | 0.97 (0.90, 1.03) | 0.31 |  |
| >median | 0.98 (0.90, 1.06)  | 0.63 |  |
|  |  |  |  |
| Fat intake (g/d) |  |  | 0.54 |
| <median | 1.01 (0.95, 1.06) | 0.82 |  |
| >median | 0.97 (0.91, 1.03) | 0.32 |  |

Abbreviations HR: hazard ratio CI: confidence interval SD: standard deviation BCAA: branched chain amino acid, NHS: Nurses’ Health Study, HPFS: Health Professionals Follow-up Study.

1Pooled HRs were calculated by pooling HRs in HPFS, NHS and NHSII using random effect models.

2Median value was used to stratify by physical activity. (HPFS 20.2, NHS 11.6, NHSII 15.0 MET-hours/wk).

Multivariable HRs were adjusted for age, smoking status (never, past, current <15 pack-years, current ≥15 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), regular aspirin use (≥2 tablets/week, yes or no), menopausal status and postmenopausal hormone use (premenopause, never, past, current, in women only), body mass index (<23, 23 to <25, 25 to <27, 27 to <30, ≥30 kg/m2), physical activity (quintile), alcohol consumption (0 to <5, 5 to <10, 10 to <15, or ≥15 g/day) and dairy calcium intake (quintile). Standard deviation (SD) was 2.59 g/d in HPFS, 1.98 g/d in NHS and 2.47 g/d in NHS II.